Thoughts, Observations, and Experiments on the Action of Snake Venom on the Blood.

WITH

An Appendix.

PROFESSOR HALFORD.

Dr P Sclater F.R.S.
with best remembrances
Thos Anderson

THOUGHTS,

OBSERVATIONS, AND EXPERIMENTS

ON THE

ACTION OF SNAKE VENOM ON THE BLOOD.

WITH AN APPENDIX.

BY

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PROŒMIUM.

The blood is both author and preserver of the body, the primogenial matter and vital spark, the first to live and the last to die, the immediate seat of the vegetative faculty of the animal, and of every other part of the body subordinate or posthumous to the blood.

HARVEY.

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THOUGHTS, OBSERVATIONS, AND EXPERIMENTS ON THE ACTION OF SNAKE VENOM ON THE BLOOD.

By GEORGE BRITTON HALFORD, M.D.

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In the year 1867, Sir James Paget communicated to the *British Medical Journal* two papers written by me—one of July 20, the other December 21. Sir James, in forwarding the last communication, wrote—"I hope you will deem it right to publish this; for the facts are very strange—so strange, that it may be well for me to add that Professor Halford, writing to me, says, that I may depend on the patience and fear of error with which he has worked at them."

I had been appointed to my present position by the late lamented Sir Richard Owen and Sir James Paget. I am pleased to say that all I then wrote, and the drawings I sent, are absolutely true; changing my "germinal matter" to the more generally adopted term "proteid." How comes it that I can demonstrate the

cells of the same character and size, as I did twenty-seven years ago? How comes it that none of the observers in India have seen these large cells? If they had looked for them at the times after death I indicated, they would have seen them, for they are, as cells, a post-mortem change, although antecedent changes in the proteids of the blood were going on, probably chemical, not to be detected with the microscope. On this most difficult point, on the interaction of the proteids of the blood, the most remarkable work on "The Chemistry of the Blood," by the late Dr. L. C. Wooldridge, must be carefully studied.

How comes it that my most urgent thought has been again directed to this subject? The answer is as follows:—

A few months ago, I heard that Mr. Martin, of Sydney, M.B., B.Sc., of the London University, had said that he thought my ideas of the action of snake venom on the blood were most probably correct. Mr. Martin had been formerly Demonstrator of Physiology at King's College, London, and is now Demonstrator of Physiology in the University of Sydney, and had since devoted himself to the study of the chemical composition of snake venom. I heard that he was coming to see me to study the physiological action on the blood and tissues. He came, and I found in him a most accomplished laboratory worker, possessing a thorough knowledge of present animal chemistry.

He gave me his papers on the subject, which truthfully record the results of his experiments, his observations, and his previous reading, and which, I think, should be known to all who are concerned in unravelling this difficult subject. The papers are:—First, "The Venom of the Australian Black Snake,"

by C. J. Martin and J. McGarvie Smith; and the second and third, Vol. XV, No. 4, 1893, *Journal of Physiology*. Of these two papers, that of the Injection of Black Snake Venom is the most important for our present investigation.

Mr. Martin, a few weeks back, visited me, bringing some black snake venom. He brought also with him a mind at the back of his retina, which is necessary for all optical enquiry. He brought also youth, a valuable adjunct, for he is only 28 years old. In addition to these requisites, we have now microscopes which will show us things clearly which we saw only darkly in those other days. The microscope I used originally was a magnificent Powell and Leland, and my drawings were done with the camera lucida. The glass I now use is Reichert's No. 1A, and with the apochromatic lenses and compensating eye-pieces, the coloration of any dye that may be used is absolutely perfect.

The Toxic Power of Snake Venom.

It has been, for a long time, the fashion to underrate the power of the poison of Australian snakes, as compared with that of the Indian cobra. In 1873 I wrote—"The death of a dog follows as rapidly after the bite of an Australian venomous snake as after the bite of a cobra;" and again, "Dr. J. Macbeth records the deaths of twenty-nine dogs which had been bitten by cobras, and to which no remedy had been applied. The average time between the bite and death in these cases is three hours and twenty-three minutes; the shortest, eleven minutes. I find that two hours and fifteen minutes is the average time between the bite

of the tiger snake (*Hoplocephalus curtus*) and death in nineteen dogs; the shortest interval being seventeen minutes."

C. J. Martin's Opinions on this Subject.

"Although the yield of poison from our Australian snakes is so small, we find that the virulence of our black snake (*Pseudechis porphyriacus*) compares very favourably with that of the cobra; that is to say, the minimal fatal dose per pound weight is, in our hands, considerably less than that given for the cobra by the Indian Snake Commission. Some idea of this virulence may be gathered from the fact, that $\frac{1}{1000}$ grain invariably kills a rabbit of 5lb. weight, when injected into a vein, in about one hundred seconds.

"The following experiments illustrate the toxic power of the poison:—

"One-tenth grain of dried black snake poison was dissolved in 5 c.cm. of 1 per cent. NaCl. solution, 0·05 c.cm. would accordingly equal $\frac{1}{1000}$ grain.

"Four rabbits, each weighing 5lb were taken, and the poison injected into the median vein of the ear. The first two received 0·1 c.cm. of the solution, and died in ninety seconds and ninety-one seconds after the withdrawal of the syringe. Two others received 0·05 c.cm of the solution ($\frac{1}{1000}$ grain), and succumbed in ninety-seven and ninety-eight seconds respectively.

"Similar experiments were performed with a solution of the venom from the tiger snake (*Hoplocephalus curtus*) prepared in a similar manner, so that 0·05 c.cm. equalled $\frac{1}{1000}$ grain. The two rabbits which received 0·1 c.cm. ($=\frac{1}{500}$ grain) died in ninety-two and one hundred and one seconds, and those which had

0·05 c.cm. (=$\frac{1}{1000}$ grain), in one hundred and four and one hundred and five seconds respectively. All four rabbits weighed over 5lb.

"The above experiments show a marked uniformity between the toxic powers of these two venoms."

The comparative weaker powers of the venom of the Australian snakes having been disproved, I now proceed to the observations I have made.

The Action of the Venom on the Blood.

In May 1852, I being then House Surgeon to the Westminster Hospital, a man was brought in at about 11 a.m. by two friends, who said he had been bitten by an adder which he had bought at Butler's Covent-Garden. He looked stupefied; his face was swollen, the tongue also was greatly swollen, and partly hanging out of his mouth: there was also great œdema of the submucous tissues of the mouth and throat. I naturally looked about these parts for the bite, but to my surprise was told he had been bitten on the index finger of the right hand; I saw two minute punctures. I sent him to bed. Leeches, fomentations, and purging relieved the œdema, and by the evening he was comparatively well. I have omitted however to say that, soon after his admission he vomited, and felt pain at the pit of the stomach. The next morning, on going round the wards, the nurse told me the man complained of pain and stiffness of the arm, and pain in the axilla. On taking off his nightshirt, I found swollen veins running up to the axilla, and to the corresponding side of the thorax, with evident ecchymosis of the whole of these regions. Subsequently, these parts underwent all the successive colour-stages of

bruising. My remarks, at the time, were—"What a wonderful effect viper poison must have on the blood-vessels or blood, or on both."

Next in the order of time, namely October 1852, came the death of the attendant at the Zoological Gardens in London; he was bitten on the nose by a cobra, and died in ninety minutes. I knew the man, and was in the Gardens the same day. The post-mortem examination was made by Mr. Marshall, and this is what he said:—"Externally, there was more ecchymosis than is generally the case, especially in the face and at the back, from the nape of the neck to the calves of the legs; the purple colour being more uniform and less mottled than usual. On dissecting off a portion of the skin over the angular artery and vein, between the root of the nose and the inner canthus of the eyes, the cellular tissue was found strongly ecchymosed. The blood was altogether dark, alkaline, and fluid, and it emitted a peculiar sour and sickly smell. The effect of this morbid poison seemed to be very much like that produced by the ingestion of prussic acid."

I must now quote from a paper read March 10, 1864, by Dr. George Harley, and published in the "Philosophical Transactions of the Royal Society of London," entitled—"On the Physical and Chemical Agents upon Blood, with special reference to the mutual action of the Blood and the Respiratory Gases." A dog was twice bitten by an African puff-adder, and died in two and a quarter hours; the post-mortem appearances are thus described by Dr. Harley:—"The tissues presented a very strange appearance, viz., numerous extravasations of blood throughout the body, some small, some large. For example, in this animal there was an

extravasation of blood into the anterior mediastinum and into the tissues of the pericardium, but no effusion into the pericardium itself. There was extravasation along all the great veins, into the cellular tissue of the pancreas, throughout the diaphragm, beneath the peritoneum, and all over the abdomen. The interior of the latter, indeed, looked exactly as if it had been sprinkled over with blood. A similar condition also existed in the subcutaneous cellular tissue. In fact, had the history of the case not been known, it would have been supposed that the animal had laboured under a severe form of purpura hæmorrhagica. In the neighbourhood of the wounds there was great swelling, as well as extravasation of brownish putrid-looking blood. Everything pointed to blood-poisoning." This is the testimony of a most accomplished physician, with whom I was well acquainted.

The next observation I have to record is, the post-mortem examination of a man who was bitten by a cobra in Melbourne in April 1867.

Dr. Mousse, then Resident Surgeon at the Melbourne Hospital, at the inquest, deposed:—"The deceased was brought to the hospital on Sunday, at half-past four o'clock in the afternoon. He was then dying, and expired soon afterwards. A post-mortem examination showed a puncture on the second finger of the left hand. The head and arms were swollen, and at the seat of the puncture the wound was dark and gangrenous. The cellular tissue of the arm and hands was infiltrated with blood-stained serum. From all the incisions made, dark fluid blood escaped. The blood was very fluid, and had escaped from its vessels into the tissues of the body. The cause of death was poison."

In addition to the above, I may state that I was present at the post-mortem examination, and (in addition) my notes tell me that all the subcutaneous tissues of the body were as full as they could hold of bloody serum; so much so that we had a bucket at each of the four corners of the table to catch the fluid. Examination of the blood showed me a strange condition of the corpuscles.

The cobra was brought to me alive about 11 p.m. the same night. It was in a light wicker basket tied round with cord. I took him to my laboratory, put pieces of sponge through the openings and poured chloroform in. When I thought him sufficiently quiet, I cut the cords, raised the lid, and inserted him bodily into a glass jar of methylated spirit. I felt sure he would be quiet enough for me to handle in the morning, when I found him to be a spectacled snake (*Naja tripudians*) five feet four inches in length.

I obtained from his glands half a teaspoonful of liquid poison, some of which I injected subcutaneously into a dog which died some few hours afterwards with the usual symptoms of snake-poison. The blood was in the same state as that of the man who had died on the previous day.

I may mention, for the benefit of the non-scientific reader, that this cobra had had his two poison fangs extracted in India, but by the time the unfortunate man met his death in Melbourne, the two next of the reserve fangs had advanced, grown, and become connected to the poison ducts, one on each side.

Becoming greatly interested, I began experimenting on dogs, and at the same time reading all I could obtain of venomous snakes in India, America, Africa, Martinique, and the Colonies. One thing struck me

as being very important, viz., the coughing or spitting of blood or bloody serum after the bite, owing to exudations through the walls of both capillaries and air vesicles.

The following case, which I was called to attend, bears upon this point:—A gentleman residing in South Yarra, near Melbourne, rang me up at about midnight in May 1868. He told me he had been bitten by a snake, that he did not want my advice, only that he wished to know if it was a poisonous snake or not. With that, he opened a parcel and let the snake, which had been cut in halves, fall upon the carpet. The fall made it, although dead, wriggle about a little. I saw the punctures on his arm, examined the head of the snake, and found it to be that of a vigorous tiger snake (*Hoplocephalus curtus*). Presently he asked leave to go on the verandah, where I heard him vomiting, and an hour or so afterwards, at his home, he coughed up into his cambric handkerchief, blood-colored sputum. I felt sure he would die, which he did, twelve hours after the bite. His intelligence remained nearly to the last. The devitalised blood (the cause and manner of which I hope to explain further on), was no longer capable of carrying on the processes of life. It was as if one were looking at St. Paul's Cathedral, and seeing it from some mysterious cause tumbling into dust. Such were my thoughts watching the passing away of this fine man. It was the first case of death from snake-poison I had seen.

The Time between the Bite and Death, and Subsequent Loss of Coagulability by the Blood.

There are many cases recorded of death within the hour, but I shall select only two in the human subject, and one of a dog for illustration.

CASE I.—Sir Joseph Fayrer, in his work, "The Thanatophidia of India," says :—"A boy, aged 12, was bitten by a cobra (*N. tripudians*), and died in half-an-hour. The heart contained fluid blood, and the blood (of the body) was fluid."

CASE II.—A man was bitten in Melbourne, December 31, 1861, and died, it was stated, in twenty minutes. The post-mortem examination was made by Mr. Rudall, F.R.C.S. Eng. He states :—"The whole blood of the body was in a fluid state, not a single clot was observed, nor did it coagulate when exposed to the atmosphere."

CASE III.—Dr. Weir Mitchell (to whose kindness to me, and to his subsequent scientific researches on the whole subject of snake-poisoning I shall have to refer) states :—"A dog was accidentally dropped into my snake-box. He was bitten in a dozen places by as many snakes, and perished in about eighteen minutes. This was the most rapid alteration of the blood with which I have met."

It has been almost universally assumed, that such rapid result must be due to a primary action of the venom on the central nervous centres. I have always held, that it is the blood which is primarily affected, and the nervous system secondarily. I am bound to show how this can possibly be in such cases as I have quoted above.

All my readers may not be physiologists, therefore, I proceed to give them some facts for their consideration.

The whole quantity of blood in an adult man is estimated to be 12 lbs. avoirdupois. The left ventricle of the heart ejects, according to various writers, from 6 oz. to 2 oz. at each pulsation. I assume a quantity between these extremes, viz. 3 oz. avoirdupois, and I take the pulsations at 70 per minute, not 72 as in health, but allowing for the probable decline of the pulse after the bite. The question is—How long will it take for the whole blood to make one circulation?

$$\begin{array}{l} \text{12 lbs. avoirdupois} = 192 \text{ oz.} \\ \text{3 oz.} \times \text{70 pulsations} = 210 \text{ oz.} \end{array} = \frac{9}{10} \text{ of a minute.}$$

So that in the case of the cobra bite above, the poisoned blood would have circulated at least thirty times, and in the case of the dog eighteen times. No wonder then, that if called to a man, he should show deadly symptoms within a very short time.

But I must defer the consideration of the time required for the destruction of the coagulability of the blood, until I have to refer to the most remarkable papers by C. J. Martin, M.B., B.Sc. Lond., that, on this subject, I have ever read. In the meantime, I will examine the condition of the blood after death from bites of the viperine and colubrine snakes. I may premise, that I have personally experimented with the poisons of these various snakes.

(1) The viperine, including the rattle-snake, the adder, the acanthophis of Australia, and the African puff-adder.

(2) The colubrine, including all Australian snakes, except the acanthophis, which may, so far as a few fangs on the upper maxillary, be regarded as an intermediate form, but that is all.

The Fluidity of the Blood after the Bites of Venomous Snakes.

Drs. Weir Mitchell and Reichert in their Researches on the Venoms of Poisonous Serpents ("Smithsonian Contributions to Knowledge, 1886") state that—

(1) "Venom exerts a powerful local effect upon the living tissues, and induces more rapid necrotic changes than any other known organic substance. It causes œdema, swelling, attended with darkening of the parts by infiltration of incoagulable blood, breaking down of the tissues, putrefaction, and sloughing."

(Compare the effects produced by the little English adder, ut supra).

(2) "When brought in contact with the vascular tissue of a warm blooded animal, it produces such a change in the capilliary blood-vessels that their walls are unable to resist the normal blood pressure, thus allow- the blood corpuscles to escape into the tissues. The lesions are not, however, analogous to those of inflammation, since in the latter process, it is principally the white blood corpuscles which emigrate from the vessels, and the blood is highly coagulable, while here the blood exudes *en masse*, and coagulates with difficulty, if at all."

Dr. C. J. Martin has repeated these experiments with Australian black snake venom, and the results were identical.*

It is not possible for me to pass over Sir Joseph Fayrer's work, "The Thanatophidia of India." There is much that he says that is entitled to great respect, but there is also much with which I cannot agree.

* *Journal of Physiology*, Vol. XV, No. 4, 1893.

However, it being a notable contribution, I proceed to make a few extracts, followed by my own comments.

Dr. Fayrer's Opinion of Professor Halford's Paper of 1867.

"A very thoughtful and suggestive paper in the *British Medical Journal* of July 20, 1867, communicated by Professor Halford, of Melbourne, rendered the investigation more interesting, as it seemed to indicate the nature of the pathological changes induced in the blood by the poison, and to point out a new direction in which to study them, as well as to suggest a rational antidote. It will be seen that the following experiments, so far as they go, scarcely confirm Dr. Halford's views. But, even admitting the probability of Dr. Halford's theory of the cause of death, I am inclined to think that it can only be of partial application. It is peculiarly applicable to those cases in which, owing to a smaller quantity, or less potent quality, of the poison having been injected, death takes place slowly, and time is allowed for blood changes to occur. But it can hardly be said to explain the cause of death in those cases where death occurs within a few minutes after the animal is bitten by a powerful snake, and where the fatal event results almost immediately, as if by shock to the nervous centres."

And he goes on to say:—"The blood itself is affected by the poison. I have not been able to detect any corpuscular changes, such as those described by Professor Halford, nor have I any exact information on the chemical changes it undergoes, or may have undergone, but

that it is altered, there can be no doubt; and in poisoning of the lower animals, at all events, by the viperidæ, its coagulability after death is generally destroyed, whilst after death by poisoning by the colubrine snakes, the blood is generally coagulated. It is to be observed, that in most recorded cases of post-mortem examinations of human beings who have died from snake-bite (whether colubrine or viperine), the blood is noted to have remained fluid after death. I cannot reconcile this with the condition of the blood in animals, which is, as I have stated, usually coagulable after death from colubrine poisoning, but fluid after death from viperine poisoning. Further examination is needed."

On referring to Fayrer, I find the conditions of the blood stated in thirty-eight cases where it was fluid after death. Of these, five were from viperine bites, and thirty-three colubrine.

In my former experiments on dogs, and in those lately performed with colubrine snakes, viz., black snake, tiger snake, and copperhead, the blood remained fluid, and showed the changes I had previously described.

Microscopical Examination of the Blood, by Dr. Fayrer and Dr. Macnamara—Cobra Poison—Pup Inoculated—Died in Six Hours.

"The blood was examined shortly after death with Professor Macnamara's $\frac{1}{20}$ and $\frac{1}{50}$ inch object glass. The red corpuscles were shrivelled and crenate. No indications existed of new cell formations containing

germinal matter, although they were most carefully sought for. The only cells which we could find were the healthy red and white corpuscles. In this case, where death occurred in six hours, and where sufficient time had been given for blood changes, I think that if the changes described by Professor Halford always take place, they ought to have been detected."

[The large cells, to the best of my belief, were seen by Dr. Fayrer and Dr. Macnamara in the blood of a fowl, but not recognised by them as those so frequently described by me.]

"A full-grown dog was bitten by a large cobra, died in twenty-six minutes. Blood examined just after death coagulated firmly.

"A half-grown domestic fowl was inoculated on the inner side of the right thigh with the poison taken from a cobra on the spot. Died in three hours.

"*Necroscopy.*—In the dog's blood, nothing remarkable was observed. The red corpuscles seemed unaltered, and the white corpuscles were present in the usual proportion. But in the fowl's blood, the appearances were remarkable. In this case, death occurred slowly —in three hours; whereas in the dog, it took place in twenty-six minutes. On carefully examining the fowl's blood with the $\frac{1}{25}$ object glass, and an A eye-piece, the following appearances were observed:— The oval red corpuscles were unaltered; but in the field of the microscope, in addition to the blood corpuscles, a number of large granular bodies were to be seen, which, after careful examination, were discovered to be contained within a distinct cell-wall. The granular bodies were coloured by an ammoniacal solution of carmine, but neither the cell-wall enclosing them nor the red corpuscles were

affected by it. As many as five or seven of these large nucleated cells were seen at one time in the field of the microscope. The granular nucleus was very distinct, and appeared to be adherent to the inner side of the delicate, though distinct, cell-wall. Although these nucleated cells were numerous, we were unable to detect the circular patches (maculæ) depicted by Professor Halford, and which he states were coloured by carmine.

"Whatever be the result of further investigation, there could be no doubt of the appearances here described, for they were peculiarly obvious. The absence of any such appearance in this dog's blood was equally certain."

Comments.

It is a pity that Dr. Fayrer and Dr. Macnamara did not more carefully examine the remarkable appearances they describe, and that they did not take the diameters of the "large cells." I made them on the average $\frac{1}{1700}$ inch. Dr. Martin, who has lately made independent measurements, comes to the same conclusion. No one who has ever seen these cells could doubt their identity with those I described. No one, as I stated in 1873, can expect to find them in blood drawn soon after death; they are a post-mortem fact, increasing in size and apparently in numbers, whilst the red corpuscles are spherical, not bi-concave, and have shed their hæmoglobin, which may frequently be seen in the form of crystals in the field.

I now extract from Sir Joseph Fayrer's valuable work some facts which bear upon the fluidity of the blood during life, and the tissues by which the blood escaped :—

By the Urine.

Subject.	Genus of the Snake.	Result.
Man	Colubrine	Recovered
,, ...	,,	Died
,, ...	Unknown	Died
,, ...	Viperine	Recovered

From other Regions.

Subject.	Region.	Snake.	Result.
Man ..	Lungs	Colubrine	Recovered
,, ..	Stomach and bowels	,,	Died
,, ..	Bowels and urine	Unknown	Died
Boy ..	Mouth	,,	Died
Man ..	Nostrils, stomach, and bowels	,,	Recovered
Woman ..	Nose, mouth, and bowels	Viperine	Recovered
,, ..	Eyes, gums, tongue nose, vagina, and from under the nails of both great toes and thumbs	Viperine	Recovered
Man ..	Mouth and nostrils	Colubrine	Died

Comment.

It was having read of similar cases in the Indian journals, long before the publication of Sir J. Fayrer's work, that made me so anxious when I saw the gentleman who had been bitten, an hour or two previously, by a tiger snake, spitting blood into his handkerchief, and from which bite he died.

It will be seen that, out of the above eight cases, four recovered. Can it be that in this way the poison had

been sufficiently eliminated and the patient saved? I have often thought that the vomiting, purging, and micturition, usually occurring in the lower animals, were similar efforts on Nature's part, but very few indeed recovered.

Influence of Rapidity of Injection of Snake Venom.

The following lucid extract is from Dr. C. J. Martin's paper in the *Journal of Physiology* already referred to. It tells us of things that were before quite unknown, and which have the most important bearing on the subject under consideration :—

"The variations in effect caused by the alterations in the rapidity of injection are very marked. So much so, that it is impossible to compare the results from different experiments, *unless the rate with which the poison is introduced is a constant factor.* Intravascular clotting is produced most readily if the dose be rapidly thrown into a vein near the heart (*e.g.*, the jugular). On increasing the time of delivery of the poison into the circulation, either by employing diluted solution, or by pressing down the piston of the syringe more slowly, the positive phase (increased coagulability of the blood) is less and less pronounced. If the rate of the injection be still further prolonged, the positive phase, if present, is so rapidly succeeded by the negative variation that this latter appears to be the only result. The negative phase becomes more and more pronounced as larger quantities of the venom are allowed to slowly enter the circulation. For slow injections I have connected a burette containing a very dilute solution

of venom in ·7 per cent. NaCl. with the canula in the vein, by a piece of rubber tube, the calibre of which was controlled by a screw clamp. With this arrangement I have been able to introduce large doses (0·005 gramme per kilo), and yet only produce inhibition of the coagulability of the blood. The discovery that the effects on the blood, after slow injections, are vastly different from, in fact exactly opposite to, those following rapid injection of the venom, explains why, in my earliest experiments, I did not obtain the same fluid condition of the blood as Halford, who used either subcutaneous injection of the venom, or else allowed a snake to bite the dog. By these methods delivery into the circulation would necessarily be slow, and comparable with results obtained by intravenous injection, only in cases in which such injection was very gradual."

Seeing and Not Seeing the Large Cells in the Blood.

In 1891, I called on Sir J. Fayrer in London, and told him I wished to show him the cells in the blood. He received me very courteously, but said that he knew little about the microscope, and had trusted to the statements of Drs. Macnamara and Lewis—the latter gentleman, the whole medical world knows, from his description of the blood of Hindoos abounding with those remarkable embryos "the filaria sanguinis hominis." Here there could be no doubt as to the capacity of the microscopic observer.

I then visited my old friend Mr. Bartlett, Superintendent of the Zoological Gardens, London, and got

three rabbits killed—one by a cobra, the second by a rattle-snake, and the third by an African puff-adder. I sent one to Professor Burdon-Sanderson, then of University College, one to Professor Klein of St. Bartholomew's, and one to Dr. Stewart, then of St. Thomas', and now of the Royal College of Surgeons, England.

Results.

In the blood of the rabbit bitten by the rattle-snake, sent to Dr. Burdon-Sanderson, *not a trace of these cells could be seen after the most careful examination.* I was there and did not see them. In the blood of the rabbit bitten by the cobra, sent to St. Thomas', the cells were in abundance, and both Dr. Stewart, then President of the Microscopical Society of London, and Dr. Greenfield, then of the Brown Institution, and now Professor of Pathology in the University of Edinburgh, saw them readily. They were also in abundance in the blood of the rabbit bitten by the puff-adder, sent to St. Bartholomew's. I was very anxious to get Dr. Klein's opinion as to what the cells were; but he said he could not understand them, and that he had never seen such appearances in any previous blood that he had examined. He was just starting for Egypt to study cholera. There the matter has rested until the fortunate arrival of Dr. C. J. Martin at Sydney.

The Origin of these Cells.

Before beginning to describe what I have myself seen and thought, I must make an extract from the

late Dr. L. C. Wooldridge's now celebrated work on "The Chemistry of the Blood," as peculiarly applicable to this part of our subject. Speaking of the possible origin of red blood corpuscles from plasma, he says:— "On the one hand the process is evidently allied to crystallization, and the discs might be regarded as a crystalline precipitate; on the other hand, they may be looked upon as imperfect cells. *Omnis cellula e cellula* is a dogma. Is it true? Are blood corpuscles and plasma discs cells, or are they crystals? Surely, if ever we shall have a borderland between 'vital' processes and ordinary physical and chemical processes, we shall find it in the blood plasma."

These cells seem to arise from the molecular or nebulous masses (of plasma) lying in the intervals of the red corpuscles. This much is certain, that as they appear, so does the nebulous matter disappear. They are at first extremely transparent, and almost invisible, requiring faith to believe in their presence. Twelve hours after the bite, they may be readily seen. At this time, without adding magenta, the macula is a bright particle on the inner wall of the cell (not a pullulation). Twenty-four hours after the bite, they are usually at their greatest size, and the macula is small. When the cells are smaller, the macula is always larger than when the cells are distended. I have lately investigated this point, and find it as it had originally seemed to me. Should now magenta be added, and a 4 mm. apochromatic objective used, with a compensatory eye-piece, the macula will be seen as a bright ruby-coloured particle. The coloured macula can also be seen with an ordinary achromatic object glass, but, necessarily, its colour will not be so pure.

What is the Poison?

This is a difficult question to answer, but it must be attacked. The most reliable opinions are those of Drs. Weir Mitchell and E. T. Reichert of Philadelphia, and those of Dr. C. J. Martin and Mr. J. McGarvie Smith of Sydney. Weir Mitchell and Reichert say:—

(1) "Venom bears, in some respects, a strong resemblance to the saliva of other vertebrates.

(2) "The active principles are contained in the liquid parts only.

(3) "Venoms may be dried and preserved indefinitely in this condition, but with a very slight impairment of their toxicity. In solution of glycerine, they will also probably keep for any length of time.

(4) "There probably exist in all venoms representatives of two classes of proteids, globulins and peptones, which constitute their toxic elements; the former may be represented by one or more distinct principles."

Drs. C. J. Martin and McGarvie Smith thus sum up their results on investigating the venom of the Australian black snake:—"The products of the secretion of the epithelial cell of the gland are—hetero-, proto-, and deutero-albumoses, and no ferment." "Our conception of the formation of these albumoses in the venom-gland of the snake is the following:—The cell, by a vital process, directly exercises a hydrating influence on the albumins supplied to it by the blood, the results of which influence are the albumoses, which we find in venom. The difference between this process and the digestion by pepsin or by anthrax bacilli is, that in the case of the gland cells of the venom gland, the hydration stops short at the albumose stage, and is not continued so as to form peptone, as is the case with the others (stomach and pancreas) mentioned. That the

protoplasm of gland epithelium is capable of exercising such a hydrating influence, we will instance the conversion of glycogen into sugar by the liver."

"It must be borne in mind, that although the proto-albumose, hetero-albumose, and deutero-albumose, which are formed by these various agencies, have so far not been chemically differentiated, they are not identical, and when submitted to that infinitely more sensitive test—the physiological one—produce vastly different results."

Is the Poison a Ferment?

Dr. C. J. Martin says not; because, unlike pepsin and trypsin, its action is not destroyed by boiling, *but it is by prolonged boiling.*

The Definition of a Ferment.

I extract the following from Waller's "Human Physiology, 1891":—

"The essential constituent of each digestive fluid is a ferment—*ptyalin* in saliva, *pepsin* in gastric juice, *trypsin* in pancreatic juices, *invertin* in intestinal juice. These and other ferments are the specific agents by which the digestive transformations of the food are effected. *They are the occult agents of modern physiology, inasmuch as they have never been isolated as definite bodies, and are recognised to be present only by the effects they produce.*" The italics are mine (G.B.H.)

I claim therefore for snake venom the rank of a powerful ferment. For, in addition to the difficulty

with which it can be destroyed, its action is far more prolonged. My belief is, that the living blood and tissues resist the action of the poison, but that at last they fail to maintain their preservative power; that the venom, once introduced into the circulation, continues its action after the temperature of the body has fallen, and continues till what should have been in normal blood (fibrin), is destroyed, its place being taken up by the large white cells I have described. This, on my part, is purely hypothetical, but it is the best I can say now. Doubtless it will be in the power of future investigators to confirm or destroy these fancies, and it will be a great result to our knowledge when something definite has been arrived at. I have the greatest hopes in Dr. C. J. Martin's future investigations.

Brainard's Description of Poisoned Blood.

Not being able to refer to "The Smithsonian Reports" of 1854, I extract the following from Nysten's "Dictionaire de Medicine," Paris 1858, which being translated, reads as follows:—"Dr. Brainard, of the State of Illinois, in causing pigeons to be bitten by rattle snakes, found:—

(1) "Change of form of the red corpuscles, by their assuming a spherical condition.

(2) "Abundance of white corpuscles grouped together in aggregated masses.

(3) "Fluidity of the blood in the cavities of the heart, resulting from the non-coagulability of the fibrin.

(4) "In mammals, hæmorrhages from the mucous membranes, and petechial discoloration of the skin."

The above observations agree with what I have recorded, and it is interesting to remark, that they were made thirteen years before my own microscopical examinations of the blood.

Experiments with Shires.

This man apparently cared nothing for venomous snakes; he would put his *bare arm and hand* into a box containing fifty snakes and pull out one, just as a fisherman would an eel from a bag of eels.

One morning, before commencing experiments with his antidote on twenty dogs, he said he would try an experiment on himself with some snakes from Gippsland, venomous without doubt. There were several gentlemen present, some of whom are still in Victoria. I told him I would not permit such a thing, but, as he insisted, I was foolish enough (I did not think till afterwards how foolish!) to tell him, to guard against deception, to pick out a certain tiger snake, one out of many that I had received the evening before from Dr. Gummow, of Swan Hill. The snake bit him on the left forearm, three inches above the wrist, and held on. He applied his remedy, and I watched him throughout the day, and certainly no symptoms of snake-poisoning supervened. Had he died, where should I have been? How could this immunity be accounted for, for nineteen out of the twenty dogs died? I was aware that he had been several times previously bitten, and once or twice nearly dead. It occurred to me, could previous inoculation have saved him? as we know now

that previous inoculations save, or greatly modify, the effects of other organic poisons. This brings us to a remarkable statement by C. J. Martin* which is: "A previous injection of small doses of black snake venom confers an immunity, so far as intra-vascular clotting is concerned, against further injections of the venom. This immunity is very speedily produced; how long it may last I am at present not in a position to say."

I have introduced these facts stated by Dr. C. J. Martin, as they may be considered side by side with the facts I have recorded about Shires.

The Indestructibility of the Toxic Powers of Snake Venom.

Dr. Weir Mitchell, in 1860, speaking of the poison of the rattle snake, says:—"Freezing has no effect; boiling has no effect; strong nitric acid, strong muriatic acid, strong sulphuric acid—each of these strong acids, after mixing with the venom and acting upon it for twelve minutes, was neutralised with liquor potassæ—each mixture, when injected into the subcutaneous tissue, produced death. When mixed with ammonia, chlorine water, iodine, soda, potash, and each mixture injected, no effect was found to have been produced on its virulence."

I repeated all these experiments with the poison of the Australian tiger snake, and found the results actually similar.

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* *Journal of Physiology*, Vol. XV, No. 4, 1893.

Influences of Long Continued Action of Methylated Spirit on the Venom of the Tiger Snake (Hoplocephalus curtus).

Copy of letter to Dr. C. J. Martin, of Sydney :—

"21st May, 1894.

"My Dear Martin,—Having some snakes' heads which had been in spirit for the last twenty-five years (the spirit had been occasionally changed), I got Mr. Price to dissect out four large glands, and gradually dry them. (All the tissues surrounding the glands were hardened, and the lenses were opaque, while the corneæ were still clear and transparent). Two days afterwards the glands were opened, and a fine yellowish-brown powder obtained. I was unable to dissolve this powder in warm water, and therefore could not use a hypodermic syringe. I then took an ordinary glass syringe, and injected the whole (one grain) into the cellular tissue of the abdomen of a dog. No bad results followed. The next day the wound was perfectly healed, and I removed the two stitches. This was three weeks ago, and he is still well. Subsequently, Mr. Price dissolved some of the dried poison in 25 c.c. of 1 per cent. KHO, filtered and then neutralised with weak HCl. A large precipitate was obtained, sufficiently free from particles to permit of its passing through the ordinary hypodermic syringe. The whole was gradually injected into the subcutaneous tissue of a rabbit. No injurious effect followed, and the little thing is as lively as ever.

"I now send you the following mixture, hoping that with your greater experience, you may be able to reproduce the power of the venom :—

"Dried snake poison - - - -	1 gr.
"KHO 1 per cent. - - - -	15 c.c.
"KHO 10 per cent. - - - -	2 min.

"This was raised once only to boiling point.

"George B. Halford."

Dr. Martin replied as follows :—

"University of Sydney,
"25th June, 1894.

"DEAR PROFESSOR HALFORD,—I made an experiment last week with your solution which, to my mind, proves conclusively that, whatever it contains, it possesses none of the toxic properties of the venom. The most delicate test I know is its effect, direct or indirect, upon the heart of mammals. I think I am not exaggerating when I say that, by this means, I could detect the $\frac{1}{100.000}$ grain of the venom.

"I neutralised your solution with HCl, and then injected the whole of it into a rabbit, meanwhile taking a tracing of the blood-pressure in the carotid artery. It produced absolutely no effect except a temporary rise in pressure, due to the addition of more fluid to the vascular system. I then injected the $\frac{1}{5000}$ grain of pure venom in the same manner to the same rabbit. In about thirty seconds the circulation stopped, dyspnœic convulsions consequently occurred, and the whole venous system and pulmonary artery and right heart were entirely thrombosed. I am sending you the curves, which will be obvious to you."

I received these curves, which are most beautifully executed. The result seems then, that such prolonged maceration in spirit had extracted the toxic properties of the venom. This is in harmony with the conclusion of Dr. Lauder Brunton, on the activity of the alcoholic extract of cobra poison, viz :—"The alcoholic extract resembles the poison itself in its activity, and in the symptoms it produces."

Is there any Antidote to the Venom?

The answer is, I think, No. Let us see what we have to contend with. The bones of the skull of a venomous snake, including both upper and lower jaws,

are so modified and articulated as to suit the muscular action necessary for the instantaneous erection of the poison fang, and to cause it to penetrate beneath the skin of the victim at the same time that the poison gland is compressed and its contents ejected. Examining the fang, it will be seen that our modern hypodermic syringe is a rough copy of the original in these serpents. No venom must be lost, the apex of the fangs must first penetrate, and subsequently, the poison be thrown in. The whole mechanism is *adapted to kill.* We can now ask—How comes this about, and who has designed it? My answer is—Some Omnipotent Power with infinite Will, to which our own finite wills are remotely allied. To those who study Nature, God is present everywhere, and I recognise Him here. Can I, or any other mortal being thwart the designs of Nature? Fable, or no fable, the following words are substantially as true to-day as they were when uttered thousands of years ago:—

"And the Lord God said unto the serpent, Because thou hast done this, thou art cursed above all cattle, and above every beast of the field; upon thy belly shalt thou go, and dust shalt thou eat all the days of thy life: And I will put enmity between thee and the woman, and between thy seed and her seed: it shall bruise thy head, and thou shalt bruise his heel."

But surely some one will say—There may be some remedy discovered. Certainly, that I sincerely hope may be; but as yet we have none.

Is Strychnine an Antidote?

I must refer to Dr. A. Mueller's work* on this subject, since he is both a scientific and enthusiastic inquirer. The following is from his book:—"The writer published his theory of the action of snake poison in May 1888, after having practised the strychnine treatment for some years, and thoroughly satisfied himself of its efficacy. In the latter part of 1888, accounts of Feoktistow's researches reached this country. His final conclusions, to the effect that snake poison is solely a nerve poison, that it does not destroy protoplasm, and has no effect whatever on the blood to which its destructive potency on animal life may be ascribed, were in complete harmony with the writer's views, in fact, a re-statement of his theory."

Comment.

The whole of the evidence gathered together in this little book tends to show that snake venom is primarily a blood poison, and that secondarily, the nervous system becomes implicated. I am not going to deny the facts of recovery stated in Dr. Mueller's book. I take them as true; but as regards the antidote, a few words must be said.

Let us suppose snake venom to be injected, and subsequently, as soon as possible, a solution of strychnine; then my experience tells me that, in spite of the spinal convulsions produced by strychnia, the venom will prevail. I do not say, don't try it; but as the instructions are given to medical men to go on and increase the dose till symptoms of strychnine poisoning result, I believe there are few medical men who

* "On Snake Poison: Its Action and Antidote," 1893.

would persist so far. For strychnine can have no effect on the action of the poison. This is not to deter others from using the remedy, but simply as a record of my own thoughts and experience on this subject.

Is Ammonia an Antidote?

No! It was never published as such by me. But we may look to the physiological effect of injecting it into the veins.

Almost instantaneously the heart increases its contractions, more especially as regards its power; at the same time, the voluntary muscles are thrown into rapid contractions, so much so, if the dose be large, that they become for a short space tetanic. The circulation is necessarily increased, and the livid lips resume their wonted colour. Frequently, consciousness is restored. With all this muscular action going on, there must be a great yielding up of carbonic acid to the blood, and its subsequent removal from the pulmonary capillaries.

This is all undeniably true, and in many cases the results have been satisfactory, and in many others there have been failures. I am forced now to say, that the application of this restorative has not had the success I formerly hoped for it. The operation of injecting solely into a vein, and not into the surrounding tissues, is an extremely delicate one for ordinary medical practitioners. This, unfortunately, has been proved; but it should no longer be so. Here, then, is another instance of failure where success was expected.

DESCRIPTION OF THE PLATES.

Plate I.

Magnified 440 diameters, making them from $\frac{1}{1600}$ to $\frac{1}{1700}$ of an inch.

The large cells, as they are seen in the blood before the addition of magenta solution. It will be observed that the whole cell consists of granular matter, with a large granular nucleus.

It is, to me, evident that these cells are the same as those alluded to by Brainard, thus :—"Abondance de corpuscles blancs se groupant en masses mamelonnés."

Plate II.

The same cells after the addition of the following solution :—

Magenta (or fuchsin)	0·1 gramme.
Absolute alcohol	2 c.c.
Distilled water -	98 c.c.

This is mixed on the slide with a drop of the blood, and, after a few minutes, a thin cover-glass gently put on.

The cells have lost all their granular contents, except the granular nucleus and a small portion of proteid matter adhering to the inner side of the cell-wall. Both are deeply stained by the magenta, and the latter is what I have called "the macula," for it is not a "pullulation."

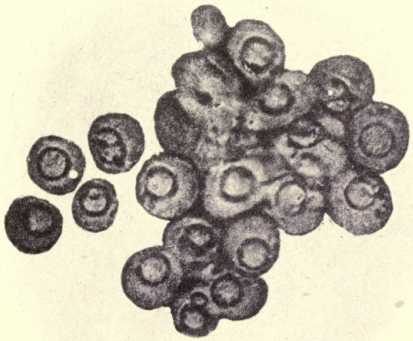

PLATE I.

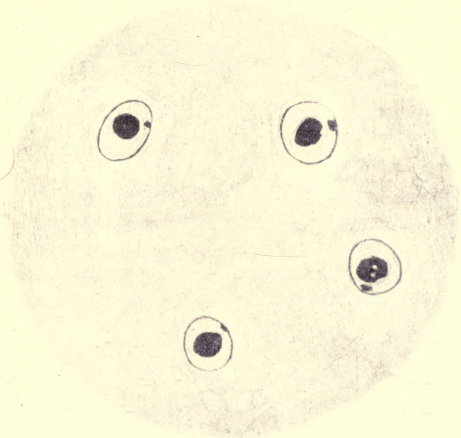

PLATE II.

PLATE III.

Plate III.

Magnified 175 diameters.

Description of the microscopic structure of the poison gland of tiger snake (*Hoplocephalus curtus*).

This is similar to that of a parotid gland. The epithelium of the alveoli is tessellated; the cells are polyhedral, with comparatively large nuclei; the nuclei are granular. The coagulated contents of the alveoli consist of débris of cells, nuclei, &c.

The tubules are distinctly lined with columnar epithelium, the nuclei being situated near the periphery of the tubule.

APPENDIX.

In the year 1869, I commenced experiments on the effects of injecting certain so-called antiseptics and disinfectants into the circulation of dogs, believing from the researches of Koch and others that we had to deal with bacteria, or the poisons they generate, in the lymph spaces and sub-mucous tissues external to the capillaries. I thought intra-venous injection the best way to get at these organisms and their products. I further commenced to inject poisons into the blood with very strange results. I have thought it right to include these as an appendix to what I have said about snake poison.

We all know how, from scattered observations pieced together by subsequent workers, great results have been obtained, notably in the science of Electricity, without which we should, in the present day, be comparatively in both physical and intellectual darkness. The beginnings of electrical science were solely from observations, and led to experiments. It is in the hope that the rough experiments I am about to record may set some of my juniors thinking, and possibly lead to a more improved system of applying the facts recorded to medical science. I have not, now, the requisite eye-sight to differentiate between the very minute organic forms, constituting bacteria.

Injections of Sulphurous Acid.

The acid used was a saturated solution of SO_2, made expressly for me by the late Professor J. D. Kirkland.

October 11, 1869.—Injected into the left external jugular vein twenty-five minims.

Result.—Breathing slightly hurried.

A quarter of an hour after, another twenty-five minims were injected.

Result.—Nothing but slightly accelerated breathing.

Between three and four hours afterwards, I injected into the same dog, using both external jugulars, more than half an ounce of the same sulphurous acid.

Result.—None other than recorded above, the dog remaining quite well and lively.

Comment.

I was naturally surprised at these results, and doubted the strength of my solution. I therefore took half a teaspoonful, and placed it in my mouth. I became nearly suffocated, the fumes arising closing my glottis, and going wherever it suited them. This is an instance of the value of practical work, for I shall never do such a foolish thing again.

In September 1875, I re-commenced these experiments under the control of our Professor of Chemistry, the late J. D. Kirkland (a tablet regretting his death, and showing his worth, may still be seen in the vestibule of our Medical School).

September 8, 1875.—At 11.50 a.m., I threw in at one injection into the left jugular vein of a full sized sheep-dog, one ounce of the saturated solution of SO_2.

Result.—The dog, on being placed on his legs, staggered a little, but soon became quiet and lay down. A quarter of an hour after this he got up, and became as lively as before the experiments.

October 12, 1875.—Half an ounce of sulphurous acid of the recognised strength was thrown into the femoral vein of a small dog.

Result.—Before the whole quantity was injected, the dog suffered as if from choking, and the breathing was much oppressed. Shortly afterwards, he quite recovered. In order to ascertain whether the acid had been oxidised in the pulmonary circulation, or had travelled on to the tissues, the following observations were made:—

Four test-tubes were taken and marked Nos. 1, 2, 3, 4.

Into No. 1, blood was taken from the ear before the acid was injected.

Into No. 2, blood was placed three minutes after the injection.

Into No. 3, blood was placed ten minutes after injecting.

Into No. 4, blood again twenty minutes after injecting.

In each test-tube was added a fragment of zinc, and then a little hydrochloric acid, at the same time a cap of paper, moistened with acetate of lead, was placed over the mouth of the test-tube. The result would be, if sulphites were present in the blood, a blackish sulphide of lead would be formed on each paper cap.

Results obtained after standing eighteen hours :—

No. 1.—Only a very slight discoloration.

No. 2.—Dark brown deposit.

No. 3.—Still darker discoloration.

No. 4.—Black deposit.

Other similar experiments were made on two other dogs, with precisely the same results, which seem to show that the sulphurous acid is not all, by any means, used up in the pulmonary circuit.

Carbolic Acid.

At this time, carbolic acid was largely used as an antiseptic and disinfectant. It was further stated, that it destroyed parasites, both animal and vegetable, and that it arrested fermentation. I therefore (October 14, 1869) made the following solution :—

Pure solid carbolic acid (Calvert's)	3 parts.
Distilled water - - - -	1 „
Glycerine - - - - -	12 „

So that m. xxv equalled 4·7 grains of carbolic acid.

Experiment I.

I injected into the femoral vein of a small dog m. xxv.

Result.—Within a few minutes, a tremor commenced in all the muscles, which passed into *clonic* spasms all over the body, from the eye-lids to the tail. The dog remained quite sensible, and in five minutes the spasms ceased. Five minutes afterwards, another

equal quantity was injected. This was followed by exactly the same symptoms, only a little more violent. In another five minutes the dog micturated, the urine smelling strongly of the acid, and shortly afterwards, ran about as usual.

Experiment II.

October 15.—A very small dog was taken, in order to see whether the symptoms described yesterday were due to the carbolic acid or to the glycerine. Twenty-five (xxv) minims of pure glycerine were injected. No effect whatever produced. Ten minutes after this, I injected another m. xx of the carbolic solution into the same vein. The same clonic spasms returned in exactly the same time, and of the same character as those of the dog experimented upon yesterday, and passed away as rapidly. There could be no doubt that the symptoms were due to the injection of the acid into the blood.

Experiment III.

October 16, 1869.—The same small dog as yesterday was injected with m. xx of the following mixture :—

Carbolic Acid - - - - -	3 parts.
Water - - - - - -	1 „
Glycerine - - - - - -	4 „

So that m. xx equalled 7·5 grains of pure carbolic acid.

Result.—Within a second or two, the same clonic spasms commenced and continued without intermission for a quarter of an hour, after which they gradually

declined, and ceased completely in half an hour. The dose seemed very severe; the pupils being, at first, widely dilated, and afterwards relaxing. All the muscles of the body, the heart included, participated in the action, but he soon completely recovered.

Effects of the Stronger Solution on the Muscular and Mucous Surfaces and on Albumen

(1) A drop or two was let fall upon the exposed surface of the rectus abdominis muscle. It became immediately bleached in the track of the acid.

(2) A little placed on the tongue was too severe for any of my students or myself to bear.

(3) A small quantity added to a prepared solution of white of egg immediately coagulated the albumen.

Comment.

It will be seen that, as with liq. ammoniæ and sulphurous acid, very large quantities can be introduced directly into the blood which cannot possibly be administered either by the stomach or lungs.

OXYGENATING BODIES.

Bromides and Iodides.

Experiment I.

One hundred grains of bromide of ammonium, dissolved in distilled water, were injected into the jugular vein of a dog within twenty-five minutes.

Result.—No bad effects. Half a fluid drachm was thrown in directly into the right ventricle of the heart. No injurious results. But when blood was taken from an artery, it seemed of a brighter scarlet, and certainly coagulated more firmly and rapidly than usual.

Experiment II.

One thousand grains of iodide of ammonium, dissolved in two ounces of distilled water, were gradually, during twenty-five minutes, thrown into the external jugular vein of another dog.

Result.—Dog perfectly unaffected.

ANÆSTHETICS.

Chloroform.

Twenty-five minims were thrown into the external jugular vein of a large dog.

Result.—Almost immediate insensibility, with greatly dilated pupils; but in one minute, consciousness was returning. Three minutes afterwards, I injected another twenty-five minims.

Result.—Immediate insensibility, with dilated pupils. I at once amputated a leg, but whilst I was sewing together the flaps, consciousness was returning, as evinced by expressions of pain.

COMMENTS.

Two things are here clearly shown :—

Firstly, that the effects of this direct injection are too evanescent, and that the ordinary inhalation is infinitely preferable.

Secondly, and this is important, that chloroform vapour will escape from the blood *if it can*, and that so long as respiration goes on, there is a great chance of a person apparently dead from chloroform being resuscitated. This I have repeatedly proved by experiments on dogs in our laboratory, by using the Cambridge Scientific Instrument Co.'s artificial respiration pump.

Æther.

EXPERIMENTS.

Twenty-five minims were injected into the femoral vein of a small noisy dog.

Result.—The dog became quite quiet, but not insensible. I then, almost immediately, injected xv m. more.*

Result.—In two seconds, he became insensible; pupils dilated. I cut off the dog's leg. He soon recovered; but the whole surface of his body and limbs remained perfectly anæsthetic for some time afterwards, not taking any notice of cutting or pinching.

* The two doses represent, approximately, half a litre of the vapour of ether at the ordinary temperature, 15·5° C., or 60° Fahr.

COMMENTS.

This obeyed the same physical law as the chloroform, becoming almost as rapidly exhaled from the lungs as it was thrown in.

Ozonic Æther.

EXPERIMENT I.

Two fluid drachms were injected into the femoral vein of a dog.

Result.—No insensibility; rather seemed happier.

About this time (1874), I had begun using the micro-spectroscope, and the year before Dr. John Day, of Geelong, had contributed several valuable papers to the Medical Society of Victoria, on the Oxidising Properties of Ozonic Æther, or Peroxide of Hydrogen.

EXPERIMENT II.

I placed some diluted venous blood in the little tube supplied with the micro-spectroscope, and at once obtained the spectrum of reduced hæmoglobin. I then removed the little cork, and added a drop or two of the ozonic æther. I then inverted the tube, so as to allow of the fluids to mix *without shaking.*

Result.—The broad dark venous band gradually disappeared, its place being taken by the two characteristic bands of the oxyhæmoglobin spectrum.

I have for the last twenty years yearly repeated the experiment for the benefit of my students. I com-

municated this to Dr. Day, and now publish his answer, the reason will be obvious:—

LETTER FROM DR. JOHN DAY.

"YARRA STREET, GEELONG,
"September 14, 1874.

"MY DEAR DR. HALFORD,—

"Many thanks for your communication regarding the spectroscopic appearance of venous blood after the addition of peroxide of hydrogen.

"I congratulate you on having made the discovery, and consider it to be one of very great importance, whether regarded from a chemical or physiological point of view.

"I have often noticed on adding peroxide of hydrogen to a solution of blood, that it has given it a bright scarlet colour, but beyond that I have not gone.

"As you know, Schönbein's theory was, that the colouring matter of the blood possessed the property of transforming ordinary atmospheric oxygen into ozone. More modern chemists would perhaps say, that the colouring matter of the blood reduces peroxide of hydrogen, and converts it into common oxygen and water, but assuming this to be the case, the oxygen is in a nascent, and consequently in an active state.

"I hope you will bring the matter before the Medical Society, or some other learned body.

"Yours faithfully,
"JOHN DAY."

Chloral Hydrate.

In May 1871, I began experimenting with chloral hydrate.

EXPERIMENT.

Injected slowly forty grains dissolved in warm water into the jugular vein of a lively middle-sized dog.

Result.—In twenty minutes he became quite insensible, the limbs were flaccid, and the pupils widely dilated. Respiration slow and deep. Circulation most feeble. Thinking he might die, I injected m. xxv of liquor ammoniæ into a vein.

Result.—Almost immediately the heart's action was quicker and more forcible. The limbs and tail became extended. The pupils contracted, and reflex acts followed touching the eyelids. Respiration soon became re-established, and the dog completely recovered.

Thinking it better to introduce the chloral more gradually, I proceeded as follows :—

Experiment.

One drachm was dissolved in one ounce of warm distilled water, and injected into the peritoneal cavity of another dog.

Result.—In three minutes he lay down, and in six minutes was quite insensible, so that I amputated both hind limbs, before he woke up, which he soon did completely.

I repeated this last experiment, and was struck by the fact that this dog also became affected in three minutes, and insensible in six minutes.

This gave me some idea of the time required for the solution to be absorbed through the peritoneal membrane, and to produce its narcotic effect on the brain.

Experiment.

Six other dogs were similarly treated, and each lay down in three minutes, and became insensible in six.

One of these dogs I opened in his sleep, and found a greater redness in the tissues than usual, such however as I had previously seen in the human body after poisoning by chloroform.

Liebreich said, chloral hydrate injected beneath the skin yields nascent chloroform by action of the alkali of the blood, and produces narcotic effects.

These experiments go a long way to confirm his view.

VEGETABLE NARCOTIC POISONS.

Acetate of Morphia.

The following mixture was made :—

Forty grains of acetate of morphia.
Acetic acid, q. s.
Warm water to 2 fluid ounces.

This was carefully neutralised with liq. potassæ.

Experiment I.

October 2, 1869, at 11.30.—Four grains of acetate of morphia were injected.

11.35.—Dog comatose, pupils much contracted.

11.40.—Injected m. xxv of liq. ammoniæ into the vein, followed by universal muscular spasms.

11.50.—Pupils dilating; answering to light.

12.—Dog quite sensible, and lying down.

12.10.—Dog running about; a little dragging of the hind legs.

Result.—Perfect recovery.

EXPERIMENT II.

October 3, at 12 o'clock.—Two grains of acetate of morphia were injected into the external jugular vein.

12.3.—Pupils contracting.

12.4½.—The dog suddenly jumped up and began running about, and apparently frightened at us.

12.15.—Injected another two grains.

12.23.—Dog much excited, whining whenever he is disturbed, and dragging the hind legs a little.

12.34.—Two more grains injected.

12.37.—Running about excitedly.

Result.—No coma was induced, and he gradually recovered.

COMMENT.

I did not inject ammonia in this case, as I wanted to get him comatose first; failing this, I allowed him to recover.

EXPERIMENT III.

Sixteen grains of acetate of morphia were injected into the peritoneal cavity of a dog.

Result.—Soon became comatose.

I then injected liq. ammoniæ into a vein.

Result.—He quickly became conscious, and soon recovered perfectly.

EXPERIMENT IV.

I now determined to leave the ammonia alone, and see how much morphia a dog could stand without any remedy at all:—

2½ grains injected into the jugular.
12 grains subcutaneously.
30 grains given by the mouth.

44½ grains within an hour and a half.

Result.—No narcotism was produced at any stage, and the dog recovered perfectly.

(From the verbatim notes of Dr. Neild, March 25, 1869.)

A solution was made of one grain of m. acet. in ten minims of distilled water.

EXPERIMENT I.

10.58.—Twenty-five minims of the solution were injected into the right jugular vein of a pup.

11.1.—He lies quite still; pupils dilated. Placed on the floor, he lies quiet and his head droops. Easily roused and made to walk.

11.4.—Slight loss of power in the hind limbs.

11.6.—Rapid breathing.

11.8.—Still easily roused, and pupils dilated.

11.16.—Barks as if in a dream.

11.20.—Slight contraction of the pupil. Drags his hind legs more.

11.23.—Two drachms of the solution, equalling twelve grains of the acetate, were injected beneath the skin.

11.25.—Still runs about, but is restless and whines.

11.57.—Half a drachm of acetate of morphia was given by the mouth.

12.50.—No narcotism, and the dog recovered.

EXPERIMENT II.

A solution was made of one grain of the acetate to fifteen minims of distilled water.

11.8.—Twenty-five minims were injected into the right jugular vein of a full-sized dog.

11.11.—Pupils alternately dilating and contracting. Dog very quiet, and walks steadily.

11.15.—Twenty minims more were injected into the same vein.

11.17.—Slight stertor; pupils contracting; lies quite still.

11.24.—Pupils more contracted; eyes sensible to touch; he lies tranquil, but not unconscious.

12.35.—Dog remains quiet, but is perfectly conscious and sensible.

Experiment III.

11.30.—Twenty minims of the same solution as used yesterday were injected into the right jugular vein of a full-grown dog.

11.32.—Staggers a little, and then sits down.

11.34.—Lies prone; pupils contracting.

11.36.—Tries to get up; breathing steady.

11.37.—Quite conscious.

Noon.—Partial paraplegia.

12.4.—Twenty minims of liq. ammoniæ were injected into the right jugular vein.

12.8.—More lively; does not drag his legs so much.

12.17.—Runs about, with but little appearance of paraplegia.

Result.—Recovered.

Experiment IV.

11.55.—Half an ounce of the same solution of acetate of morphia, equalling twelve grains of the acetate, were injected into the peritoneal cavity of a dog.

Noon.—Panting, and the pupils contracting and expanding.

12.17.—Cannot walk ; great paraplegia.

12.21.—Twenty minims of the liq. ammoniæ were injected into the left jugular vein.

Result.—The heart's action was immediately increased.

12.24.—Pricked his ears and looked more lively.

12.26.—Walked, and tried to run.

12.35.—Runs about and jumps. He recovered perfectly.

Similar experiments, with the assistance of Dr. O. V. Lawrence, with even larger doses, were performed, and always with the same result as before described.

Comment.

As this Appendix has been written to record facts really ascertained, I think it very profitable to make the following extract from Dr. A. W. Blyth's work on "Poisons," London, 1884:—

"Action of Morphine Acetate on Dogs.

"From 1½ to 7·5 grains injected into the circulation of a dog, shows its effect almost immediately. The dog becomes uneasy, and moves its jaws and tongue as if some peculiar taste were experienced. It may bark or utter a whine, and then in a minute or two falls into a profound sleep, which is often so deep that while it lasts—usually several hours—an operation may be performed. In whatever attitude the limbs are placed, they remain. The respiration is rapid and stertorous, and most reflex actions are extinguished. Towards the end of the sleep, any sudden noise may startle the animal, and when he wakes, his faculties are evidently confused. A partial paralysis of the hind legs has often been noticed, and then the dog, with his tail and pelvis low, has something the

attitude of the hyena. If the dose is larger than from 31 to 46 grains, the symptoms are not dissimilar, save that they terminate in death, which is generally preceded by convulsions."

There is a great similarity of symptoms described in the extract to those resulting from my own experiments. But, strange to say, the main difference is, that after injecting 44½ grains, I could not produce any coma, neither were there any death-like symptoms or anything approaching thereunto.

In man, as we all know, no such quantities as stated above can be injected, and we also know that the action of morphia on individuals is different. A small dose in one will produce a sound sleep; in another, restlessness, and not a wink of sleep all night. These are the idiosyncrasies which are so multiple in the human race. The higher the mental development, the more varied are the characteristics of the individual. The lower we go down, the more do these individual attributes disappear, till at last there is not much difference between one frog and another, or between one wasp and another.

But there are good tempered dogs and bad tempered dogs; intelligent dogs and stupid dogs. The fidelity of the dog is proverbial. Now, this fidelity is the result of mental organisation inherited, and of antecedent cerebral organisation.

A few words, therefore, are necessary to explain, if possible, the difference of the action of vegetable poisons, such as morphia and belladonna, on dogs and man.

(1) There is very little difference between the ganglia at the base of the brain, or their connections with other parts, or with the organs of special sense

in man and dog. But when we compare their cerebral hemispheres, the difference is great indeed. In man, the sulci are very deep between the convolutions, for extension of the grey matter and the corresponding increase of blood supply. The following extract from Chaveau's "Comparative Anatomy" will be interesting before I proceed further with this seemingly difficult subject:—

EXTRACT.

"It has been attempted to establish in the predominance of the encephalon the cause of the development of the intelligence, and that the best measure of this predominance is really the relation of the spinal axis to the encephalic mass. The relations differ notably in each of the following species:—In the dog 1 : 5·14, cat 1 : 3·75, sheep 1 : 2·60, ass 1 : 2·40, pig 1 : 2·30, horse 1 : 2·27, ox 1 : 2·18."

According to Quain's "Human Anatomy," the relation of the spinal cord to the encephalon in man is as 1 : 38.

We have these further facts to help us on.

I conceive, therefore, that in man the cerebrum is more deeply irrigated with poisoned blood than can be the case in the dog, and consequently, its myriads of cells must suffer from more intimate and prolonged action of the poison than in the dog; hence, probably, the more overwhelming annihilation of function, resulting in death.

This attempted explanation applies also to the action of belladonna and atropine, which next follow:—

EXPERIMENT V.

March 26, 1869.—This experiment was devised to see accurately what was the effect of the injection of ammonia had upon the Heart itself.

The assistants in this were Dr. Neild and Dr. Wooldridge.

It will be seen that, at that time, I had no Cambridge Artificial Respirary Pump; but had to rely upon an ordinary pair of bellows, into which, when needed, I could pour chloroform, so as to produce insensibility in the dog.

To a fine large dog, chloroform was administered, and when under its influence, the anterior part of the sternum, and some portions of the cartilaginous ends of the ribs, were removed to show the contents of the thorax. Artificial respiration was kept up by Dr. Wooldridge. Half a drachm of the liquor ammoniæ was injected by myself into the left external jugular vein.

Result.—In not less than ten seconds, the heart's action became more forcible and rapid.

Ten minutes afterwards, injected the same quantity into the external jugular vein.

Result.—Same effects, and none other.

After waiting fifteen minutes, the same quantity was injected into the right ventricle of the heart.

Result.—More instantaneous, but the same results as before; the dog becoming conscious, more chloroform was put into the bellows.

Fifteen minutes afterwards, the same amount was thrown into the left ventricle of the heart.

Result.—Instantaneously, the muscles of the extremities were extended; respiratory efforts were forcibly made. After this, he perfectly recovered. But I went further, and injected into the left ventricle twice the amount of the solution of ammonia, and

each injection was followed by exactly the same symptoms. The thorax and abdomen had been exposed for one hour and twenty minutes, and the heart began gradually to fail, and the dog was allowed to die.

The details of this experiment gives an opportunity of recording my sincere thanks to Dr. Wooldridge, formerly of South Yarra, and who now, I hope and believe, is still well at an advanced age, in the Isle of Wight. He was the first gentleman in our profession whom I called upon, on the night when that unfortunate man visited me, and whose case I have briefly recorded (page 13). He willingly came with me, and attended poor Mr. Drummond till his death. Since that night we have ever been fast friends, greatly to my benefit. And now, strange to say, I have to deplore, with all physiologists, the death of his nephew, Charles Leonard, whose works I have alluded to in the part of this little essay on snake poisoning.

Belladonna and Atropine.

(From Dr. O. V. Lawrence's Notes.)

2 p.m.—One fluid ounce of tincture of belladonna was given to a dog.

Result.—Twenty minutes afterwards, the pupils were dilated, and ten minutes later they were fully dilated. There was curling of the upper lip, but no other symptoms.

2.55.—Two ounces of the tincture were then given.

Result.—No effect.

3.10.—One drachm of extract of belladonna was then given.

Result.—The dog seemed to relish it.

4.—Dog drowsy; staggers when walking; began to vomit; afterwards, barking at objects supposed to be on the walls, evidently delirium, as happens with man after taking large doses of belladonna.

5.—The dog now remaining perfectly non-comatose; but with greatly dilated pupils, and still barking at imaginary objects. I then gave him 15 grains of atropine by the mouth, and, it producing no further effect, injected another 15 grains beneath his skin.

Result.—No death, but perfect recovery

Comment.

I thought if I proceeded further I should not be able to afford it. The atropine in Melbourne then cost £1 1s. a drachm, and the tincture and extract were proportionately dear; so I let the hardened sinner go till another day, but in the meantime forgave him and kept him.

VEGETABLE IRRITANT.

Ergot of Rye.

It has long been known that this fungus, administered to the females of the lower animals, or to women, produces contractions of the involuntary muscular fibres of the uterus; and also of the involuntary fibres of the bladder, of the intestinal canal, of the smallest bronchial tubes, and, probably, of the muscular coats of the blood-vessels. Hence, it has been administered with great benefit in cases of lingering labour, when the cause has been only inertia of the uterus. Also, it has been useful in hæmorrhage from the uterus, more particularly in post-partum hæmorrhage. In bleeding from the lungs, its beneficial effects have been recorded.

From the records of medical science there is no doubt that, in the hands of a skilful practitioner, this is a very valuable aid to "obviate the tendency to death;" but at the same time, in the hands of an unskilled practitioner, it is a very dangerous agent.

I thought that, possibly, cases might occur in which an instantaneous action of the drug might be necessary. I therefore injected a solution of the drug with the following results :—

Experiment.

(From Dr. O. V. Lawrence's Notes.)

September 7, 1875, at 11.10 a.m.—Two fluid drachms of the extractum ergotæ liquidum were injected into

the right jugular vein of a middle-sized bitch, heavy in pup.

Result.—Immediately after the injection she micturated, and about eight minutes after, she had an evacuation.

11.30.—An additional four drachms of the ex. erg. liquid. were thrown into the left jugular vein.

Result.—Immediately on being placed on her legs, she began to stagger; this continued for some time. She then lay down; some spasms of the abdominal muscles were noticed, which soon passed off. Respiration easy, but quick. Heart's action quiet, but irregular.

Noon.—Bitch quiet, lying down. Respiration more regular.

1 p.m.—Still quiet, but no specific effect of the ergot.

2.0.—Very sick; but in about an hour got much better.

7.0.—Lively, and running about.

September 8.—Some time in the night the bitch had pupped, passing five, all dead.

7 a.m.—Another pup was passed.

9.0.—Another pup. Bitch very lively, and takes her food.

The pups appear about five or six weeks old. No sign of hair on the skin, and the claws were not fully formed.

THE INFLUENCE OF AMMONIA ON THE MUSCULAR FIBRES OF THE HEART.

It has been universally acknowledged by physiologists, that irritation of a nerve by ammonia vapour does not cause the muscle which it supplies to contract; but abundance of evidence has come forward to show that the application of ammonia to the muscle itself gives rise to immediate contraction, more or less prolonged.

The following experiment was recently made by Mr. Price :—

A rabbit was injected with $\frac{1}{1000}$ grain of tiger-snake poison into the external jugular vein. Death took place within one minute. On opening the chest, the heart and arterial vessels were found filled with clots. The movements of the ventricles were insufficient to get rid of their burden. The movements getting slower and slower, the apex was cut off, and a drop or two of a weak solution of carbonate of ammonia let fall into the opened ventricles. Immediately increased contractions of the ventricles took place.

This is in harmony with what Dr. Sydney Ringer has stated of the influence of ammonia on the muscles themselves, rather than on the nerves; and, therefore, this experiment agrees with what I have previously said on the effects of the intra-venous injection of ammonia.

CONCLUSION.

I have first to thank Dr. O. V. Lawrence for having so constantly assisted me in the examination of the blood after snake poisoning, and for noticing the time of the appearance of the corpuscles shown thereon, and ascertaining their magnitudes; also, as the Appendix shows, his records of many experiments I made of injecting poisons, &c., into the circulation. To Dr. Neild I have also to give my sincere thanks for assistance in experiments with chloroform, morphia, ammonia, &c. To Mr. Charles Price, also, I am indebted for great and willing assistance in the experiments I have recently made.

Since finishing the Appendix, I have received the last number of the "Annales de l' Institut Pasteur," containing—

CONTRIBUTION TO THE STUDY OF THE VENOM OF SERPENTS: IMMUNITY OF ANIMALS AND TREATMENT OF THE BITE.

By Dr. A. CALMETTE.

From the Laboratory of M. Roux, of the Pasteur Institute.

The paper is so important, that I have thought it necessary to make several extracts, in order to bring the subject up to date.

The snakes used were—the Cobra of India and Cochin China; the Tiger snake; the Black snake of Australia; and the Viper of France.

"Immunity against a dose of venom, usually mortal to fresh animals, can be obtained in the following manner:—If we inoculate under the skin of a rabbit 2 milligrammes of cobra poison, a dose capable of killing in less than two hours; and if, twenty minutes afterwards, we inject chloride of lime diluted to $\frac{1}{60}$ around the poison wound, and in various parts of the body, the rabbit thus treated resists the action of the poison, after a transient illness. It falls away at once, and continues to do so during the following six or eight days, and then completely re-establishes itself.

"If, after a fortnight's rest, $\frac{1}{2}$ milligramme of the venom is injected, it does not succumb. This rabbit is thenceforth vaccinated against this dose of $\frac{1}{2}$ milli-

gramme, which kills within eight or twelve hours all the other non-vaccinated rabbits.

"Finally, certain substances, such as hypochlorite of lime and chloride of lime, *without mixing with venom*, injected in small quantities for four or five consecutive days under the skin of rabbits, produce without fail the refractory state. The animals thus treated can, after six days, resist a mortal dose.

"Thus I have given immunity to rabbits, guinea-pigs, and to one dog. Operating with precaution, and weighing regularly the animals so as to let those who fall in condition rest, it is easy to succeed in making them support truly colossal quantities of pure venom. I have rabbits, and have had them for the last eight months, which have each received from 30 to 35 milligrammes of cobra poison, and are now in perfect health."

Properties of the Blood Serum of Animals which have received Immunity.

"The serum of animals which have received immunity against the venom by either of the preceding methods, possesses similar properties to those which MM. Behring and Kitasato, Roux and Vaillard, have established for the serum of animals against the poisons of tetanus and diphtheria.

"*The serum of a rabbit which has been rendered proof against the venom of the cobra or the viper, acts exactly in the same way with the venoms of the Australian snakes.*"

Chloride of Lime.*

Experiments.

"The solution used is in the proportion of 1 to 12. At the time of injecting, 5 c.c. are further diluted with 45 c.c. of water.

First Series.

"(1) A *control* experiment. A rabbit, weighing 1·940 kilogramme, was inoculated with 1 milligramme of cobra venom under the skin of the right hind foot at 11 a.m. Died at 2.45 p.m.

"(2) A rabbit, weighing 1·775 k., was inoculated with the same amount of venom, and in the same part. Fifteen minutes afterwards, 8 c.c. of the diluted chloride of lime solution were injected in four places around the bitten part, and in the right thigh. Cured.

"(3) Rabbit weighing 1·640 k. Same treatment as No. 2. Cured.

"(4) Rabbit weighing 1·900 k. One milligramme into the foot of the right hind limb. Half an hour afterwards was treated with 8 c.c. of the solution. Died eight days after the inoculation; wasting away, with paralysis of the hind limbs, and diarrhœa. No specific lesion found at the autopsy.

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* The ordinary bleaching powder, a compound of hypochlorite and chloride of lime will suffice.—G. B. H.

"Hypochlorous acid yields fourteen-fifteenths of its chlorine in the form of chlorine gas—one of the most efficient of known disinfectants."—Attfield.

Second Series.

"(1) A *control* experiment. A rabbit, 1·800 k. Two milligrammes of cobra poison into the muscles of the right thigh at 11 a.m. Died at 3.50 p.m.

"(2) Rabbit, 1·770 k. Two milligrammes injected into the intra-muscular tissue of the right thigh. Twenty minutes afterwards, 8 c.c. of the chloride of lime solution were injected into eight different places in the right thigh and flank. Cured.

"(3) Rabbit, 1·800 k. The same inoculation at 11.12 a.m. Treated twenty-five minutes afterwards with 8 c.c. of the diluted solution. Died the following night.

"(4) Rabbit, 1·720 k. The same inoculation at 11.18 a.m. Treated thirty minutes afterwards with 10 c.c. of the solution. Died during the following night.

"(5) Rabbit, 1·820 k. Same inoculation at 11.20 a.m. Treated thirty minutes afterwards with 12 c.c. of the solution. Cured.

Third Series.

"(1) Rabbit weighing 1·920 k. Inoculated with 2 milligrammes of venom. Ten minutes after, 1 centigramme of morphine was injected under the skin of the belly. Half an hour after this, 8 c.c. of the lime solution were injected. Cured.

"(2) Rabbit, weighing 1·680 k. Inoculated as the last with 2 milligrammes of poison. Ten minutes after, 1 centigramme of morphine injected under the skin.

Forty minutes after this, 10 c.c. of the lime solution were injected. Cured.

Treatment by the Immunity-Serum.

"The serum used was obtained from five rabbits, which had been rendered proof against the action of from 20 to 26 milligrammes of cobra venom.

"(1) Rabbit, weighing 1·870 k. Inoculated in the left foot with 1 milligramme of venom. *Half an hour afterwards,* a subcutaneous injection of 6 c.c. of the immunity-serum under the skin of the abdomen. Cured.

"(2) Rabbit, weighing 1·780 k. Inoculated with 1 milligramme of venom. One hour after, 6 c.c. of the serum injected, half under skin and half into the peritoneal cavity. Cured.

"(3) Rabbit, weighing 1·830 k. One milligramme of venom injected. One hour and a quarter afterwards, 6 c.c. of the serum under the skin. Cured.

"(4) Rabbit, weighing 1·550 k. One milligramme of venom injected. One hour and twenty minutes afterwards, 6 c.c. of the serum injected under the skin. Dead after eight hours.

"(5) Rabbit, weighing 1·900 k. One milligramme of venom. One hour and thirty-one minutes after, 8 c.c. of the serum. Cured.

"(6) Rabbit, weighing 2·220 k. One milligramme of venom injected. Treated one hour and seventeen minutes afterwards by an injection of only 2 c.c. of serum from a rabbit which had received in all 26 milligrammes of cobra venom. Cured.

"Half a c.c. of this serum, added to 1 milligramme of cobra venom, renders the latter harmless.

"(7) A *control* experiment. A rabbit, weighing 2 kilos, receiving at the same time as the others 1 milligramme of the cobra venom, but without any treatment, was dead in less than three hours.

"(8) A guinea-pig, weighing ½ kilo, was inoculated, under the skin of the right thigh, with 1 *milligramme of the venom of the European viper.* Five minutes afterwards, 2 c.c. of the *serum of the rabbit* were injected into the peritoneal cavity. Cured."

Elsewhere Dr. Calmette says:—

"Since this therapeutical serum is capable of destroying the toxic property of venom, in such extremely sensitive animals as the rabbit and the guinea-pig, may we not be justified in thinking that it would be efficacious in man?

"It is necessary, therefore, to make experiments as soon as possible, to enlighten us as to the practical value of this method. The only difficulty that presents itself is, to procure a considerable quantity of divers venoms, so as to render immunity to large animals, as is now done readily with diphtheria and tetanus. This difficulty passes away in countries were venomous snakes abound, as in Australia, the Cape of Good Hope, and above all in India, where, according to the statistics of the British Government, more than twenty-two thousand people succumb annually to the bite of these reptiles.

"A preventative and therapeutical serum against the venom of the cobra or tiger snake, will be equally effective against the venoms of the viper and black snake.

"In order that I may make experiments on a larger scale, I appeal to my fellow-workers who might be able to procure me these venoms, either dry or preserved in pure glycerine. Having thus prepared a large quantity of therapeutical serum, I will gladly place it at the disposition of medical practitioners in the Colonies liable to use it."

COMMENT.

I had already asked my friends in the country to get, during the coming summer, all the snakes' heads they possibly could; and now I ask the readers of these pages to request all their country friends to do the same, with these precautions—don't go and look for the snakes, you will find them on your road; then having rendered the snake *hors de combat*, cut through his neck about an inch or so behind his head; put the head in a parcel, and send it by post to me at the University. I will extract all the poison (pure) from the glands, and send it on to Dr. Calmette. By these means, a great reciprocal work will be commenced between India and Australia. I now pass to what he says as regards—

The Treatment of a Man Bitten by a Venomous Snake.

"(1) Place, if possible, an elastic ligature moderately tight between the bite and the root of the limb, so as to prevent absorption of the poison.

"(2) Inject, at once, into the wound, and all round about, 20 to 30 c.c. (1 oz. or more) of a recently made solution of the bleaching powder.*

"(3) Remove the ligature as soon as the injections have been made. Wash the wound with an abundance of the concentrated solution of the bleaching powder.

"It will be advantageous to sustain the heart's action, by injecting a feeble dose of morphia (about $\frac{1}{7}$ grain) or caffein subcutaneously.

"There is no inconvenience produced by injecting the diluted solution, either into the cellular tissue, or amongst the muscles. These injections are never painful, and never produce sloughing. The injections of immunity-serum will be more preferable. They should be, in the future, the veritable treatment of snake-bite. This is the practical result which we have always had in view, and hope we have attained."

Comment.

I asked, on page 27, of snake venom—Does it contain a ferment?

Dr. Calmette says:—"That 3 drops of a solution of the chloride of lime powder (bleaching powder) are sufficient to destroy, in a test-tube, the activity of 1 milligramme of cobra venom, or of 10 milligrammes of viper venom, dissolved in 1 c.c. of water."

This is a very extraordinary statement, and points, probably, to the existence of a ferment in snake poison;

* 1 in 12 of water. When required, dilute 5 c.c. of this with 45 c.c. of water.

for a few drops of the solution immediately arrests the action of ptyalin.

As regards its action on pepsin, plus the necessary amount of hydrochloric acid, it at first hinders the digestion of fibrin, but soon fails in the presence of the acid, which is the necessary accompaniment to the ferment. It is further astonishing, that so small an amount of free chlorine should have so powerful an effect, whereas, as stated by Weir Mitchell, the strongest acids, nitric, &c., cannot destroy the activity of rattle-snake venom; neither have they any destructive power, as I have myself seen, over the venom of the tiger snake.

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